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Search Results -

Terms	Documents
(L1 and $block adj1 polymer)	16

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L2	L1 and 424/450.ccls.	246	L2
L1	liposome adj10 enzyme	1431	L1

END OF SEARCH HISTORY

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Search Results -

Terms	Documents
L2 and (424/450).ccls.	12

Database:
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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L3	L2 and 424/450.ccls.	12	L3
L2	(pluronic$ or poloxamer) same enzyme	505	L2
L1	(liposome or vesicle) same (pluronic$ or poloxamer) same enzyme	16	L1

END OF SEARCH HISTORY

L3: Entry 10 of 16 File: USPT Sep 4, 2001

DOCUMENT-IDENTIFIER: US 6284267 B1
** See image for Certificate of Correction **
TITLE: Amphiphilic materials and liposome formulations thereof

Brief Summary Text (8):
The need for and importance of a functional barrier is well illustrated by potential applications of liposomes in enzyme replacement therapies for inherited metabolic diseases, in other therapies using bioactive peptides and proteins, and in hemoglobin-based blood substitutes. The safety and efficacy of therapeutic/bioactive proteins depends upon their ability to overcome metabolic and transport barriers and reach the target site in a biologically active form. This in turn is dependent on the route for administration.

Detailed Description Text (12):
Several illustrative structures are shown in FIG. 7 and FIG. 8. These incorporate glycerol or pentaerythritol residues either as polymer branching points for providing functional groups within the polymer residue, or for attaching multiple lipid residues. Branching or multiple functional groups within the polymer may be provided by polyols and their block polymers, by hydroxy- and amino acids and peptides. The functional groups may be attached directly or via linkers/spacer residues to antigens, antibodies and other pendant ligands.

L2: Entry 213 of 246 File: USPT May 21, 1991

DOCUMENT-IDENTIFIER: US 5017501 A
TITLE: Preparation of uniformly sized liposomes encapsulating an aqueous liquid

Detailed Description Text (2):
The present invention provides methods for the preparation of uniformly sized populations of marker or drug encapsulating liposomes. The following examples illustrate practice of the invention. Example 1 relates to a side-by-side comparison of liposome sizes obtained as a function of the size beads used during preparation and as a function of vortexing time. Example 2 relates to the preparation of vortexed liposomes using a digoxigenin conjugate lipid and entrapping a fluorescent marker. Example 3 relates to the preparation of vortexed liposomes using a digoxigenin conjugate lipid and entrapping an enzyme. Example 4 relates to the preparation of vortexed liposomes entrapping a drug. Example 5 relates to the use of vortexed liposomes in an immunoassay.

Current US Cross Reference Classification (2):
424/450

L3: Entry 13 of 16 File: USPT Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700482 A
TITLE: Process for the preparation of a liposome dispersion under elevated pressure contents

Brief Summary Text (20):
The therapeutic use of liposomes as carriers especially of lipophilic pharmaceutical active ingredients is known. Liposomes have also been proposed as carriers of other lipophilic substances having biological activity, such as proteins, for example antibodies or enzymes, hormones, vitamins or genes, or, for analytical purposes, as carriers of labelled compounds.

Brief Summary Text (47):
In addition to the water-soluble excipients, the liposome dispersion may comprise further excipients that can be used for liquid pharmaceutical formulations, which excipients increase the water-solubility of the mentioned active ingredients, for example emulsifiers, wetting agents or surfactants, especially emulsifiers such as oleic acid, non-ionic surfacants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethyleneglycol400 stearate, polyethylene glycol 2000 stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronic.RTM. type (Wyandotte Chem. Corp.) or the Synperonic.RTM. type (ICI).

L2: Entry 200 of 246 File: USPT Mar 2, 1993

DOCUMENT-IDENTIFIER: US 5190762 A
TITLE: Method of administering proteins to living skin cells

Brief Summary Text (33):
In a few laboratories, liposomes have been used in the topical delivery of drugs, but not of enzymes and, in particular, not of DNA repair enzymes. The reports of encapsulation and topical drug delivery include:

Brief Summary Text (35):
The use of pH sensitive liposomes to mediate the cytoplasmic delivery of calcein and FITC dextran has been described in the following references: Robert Straubinger, Keelung Hong, Daniel Friend and Demetrios Papahadjopoulos, "Endocytosis of Liposomes and Intracellular Fate of Encapsulated Molecules: Encounter with a Low pH Compartment after Internalization in Coated Vesicles," CELL, volume 32, pages 1069-1079, 1983; and Robert Straubinger, Nejat Duzgunes and Demetrios Papahadjopoulos, "pH-Sensitive Liposomes Mediate Cytoplasmic Delivery of Encapsulated Macromolecules," FEBS LETTERS, volume 179, pages 148-154, 1985. Other discussions of pH sensitive liposomes can be found in chapter 11 of the book CELL FUSION, edited by A. E. Sowers, entitled "Fusion of Phospholipid Vesicles Induced by Divalent Catins and Protons" by Nejat Duzgunes, Keelung Hong, Patricia Baldwin, Joe Bentz, Shlomo Nir and Demetrios Papahadjopoulos, published by Plenum Press, N.Y., 1987, pages 241-267. See also Ellens, Bentz and Szoka, "pH-Induced destablization of phosphatidylethanolamine-containing liposomes: role of bilayer contact," BIOCHEMISTRY, volume 23, pages 1532-1538, 1984, and Bentz, Ellens and Szonka, "Destabilization of Phosphatidylethanolamine-Containing Liposomes: Hexagonal Phase and Asymmetric Membranes", BIOCHEMISTRY, volume 26, pages 2105-2116, 1987. None of these references discusses or suggests the use of pH sensitive liposomes to topically administer DNA repair enzymes to human skin.

Brief Summary Text (52):
In comparison with prior art methods, the delivery system of the invention has the advantages of requiring high enzyme concentration only within the liposomes and not in the general exterior of the cells, and of delivering the enzyme while preserving the integrity of the target cells. Also, by suitable modifications of the liposome membranes, the liposomes can be made to bind to specific sub-populations of cells, thereby increasing the efficiency and/or specificity of enzyme delivery. As result of these improvements, the invention allows DNA repair enzymes to be used clinically, either before or after exposure to ultraviolet light, to help combat skin cancer caused by UV-damaged DNA in both normal individuals and patients suffering from xeroderma pigmentosum.

Brief Summary Text (62):
As discussed above, the present invention relates to 1) a method for purifying DNA repair enzymes through the sequential use of a molecular sieve chromatography column and a nucleic acid affinity column, and 2) the use of liposomes to administer DNA repair enzymes to living cells.

Brief Summary Text (72):
With regard to the administration aspects of the invention, the liposomes which are used to administer the DNA repair enzymes can be of various types and can have

various compositions. The primary restrictions are that the liposomes should not be toxic to the living cells and that they should deliver their contents into the interior of the cells being treated.

Brief Summary Text (73):
The liposomes may be of various sizes and may have either one or several membrane layers separating the internal and external compartments. The most important elements in liposome structure are that a sufficient amount of enzyme be sequestered so that only one or a few liposomes are required to enter each cell for delivery of the DNA repair enzyme, and that the liposome be resistant to disruption. Liposome structures include small unilamellar vesicles (SUVs, less than 250 angstroms in diameter), large unilamellar vesicles (LUVs, greater than 500 angstroms in diameter), and multilamellar vesicles (MLs). In the examples presented below, SUVs are used to administer DNA repair enzymes. SUVs can be isolated from other liposomes and unincorporated enzyme by molecular sieve chromatograpy, which is precise but time consuming and dilutes the liposomes, or differential centrifugation, which is rapid but produces a wider range of liposome sizes.

Brief Summary Text (80):
The liposomes of the present invention are prepared by combining a phospholipid component with an aqueous component containing the DNA repair enzyme under conditions which will result in vesicle formation. The phospholipid concentration must be sufficient to form lamellar structures, and the aqueous component must be compatible with biological stability of the enzyme. Methods for combining the phospholipid and aqueous components so that vesicles will form include: drying the phospholipids onto glass and then dispersing them in the aqueous component; injecting phospholipids dissolved in a vaporing or non-vaporizing organic solvent into the aqueous component which has previously been heated; and dissolving phospholipids in the aqueous phase with detergents and then removing the detergent by dialysis. The concentration of the DNA repair enzyme in the aqueous component can be increased by lyophilizing the enzyme onto dried phospholipids and then rehydrating the mixture with a reduced volume of aqueous buffer. SUVs can be produced from the foregoing mixtures either by sonication or by dispersing the mixture through either small bore tubing or through the small orifice of a French Press.

Brief Summary Text (82):
DNA repair enzymes incorporated into liposomes can be administered to living cells internally or topically. Internal administration to animals or humans requires that the liposomes be pyrogen-free and sterile. To eliminated pyrogens, pyrogen-free raw materials, including all chemicals, enzymes, and water, are used to form the liposomes. Sterilization can be performed by filtration of the liposomes through 0.2 micron filters. For injection, the liposomes are suspended in a sterile, pyrogen-free buffer at a physiologically effective concentration. Topical administration also requires that the liposome preparation be pyrogen-free, and sterility is desirable. In this case, a physiologically effective concentration of liposomes can be suspended in a buffered polymeric glycol gel for even application to the skin. In general, the gel should not include non-ionic detergents which an disrupt liposome membranes. Other vehicles can also be used to topically administer the liposomes. The concentration of the enzyme in the final preparation can vary over a wide range, a typical concentration being on the order of 50 ug/ml. In the case of pH sensitive liposomes, lower concentrations of the DNA repair enzyme can be used, e.g., on the order of 0.01 to 1.0 ug/ml for liposomes administered to cells internally. In case of topical application, higher liposome concentrations are used, eg., ten or more times higher.

Brief Summary Text (84):
The topical administration of liposome encapsulated DNA repair enzymes has been considered until now, but it is recognized that this invention has a more general application in the topical delivery to living skin of a wide variety of

biologically active proteins to achieve a biological effect.

Detailed Description Text (36):
(B) Endonuclease V activity. The endonuclease V activity assay described in Example 1 was used to measure active enzyme in the liposomes. The liposome preparation was added to duplicate assays, one of which contained 1% Triton X-100 to dissolve the liposomes. The liposome preparation was added to duplicate assays, one of which contained 1% Triton X-100 to dissolve the liposomes. Comparison of the activity between intact and dissolved liposomes served as a measure the amount of active enzyme entrapped in liposomes. FIG. 2 illustrates the type of results achieved with this assay protocol.

Detailed Description Text (44):
(A) Enzyme concentration. Concentration of the enzyme entrapped in liposomes was measured by enzyme-linked immunosorbent assay (ELISA). Liposomes were diluted to an optical density at 600 nm of 1.0 in 0.1 ml PBS and 25 mM octyl-beta-D-galactopyranoside to dissolve the liposomes. Fifty ul was then diluted in duplicate into 0.2 ml coating buffer (50 mM sodium bicarbonate, pH 9.6, 0.1 mg/ml thimersol) and serially diluted 1:1 down columns of wells in a 96-well microtiter plate. Standards of purified endonuclease V at 5 ug/ml in PBS/octylgalactopyranoside were identically prepared. After overnight incubation at 4.degree. C., the wells were washed with 50 mM Tris, pH 8, 150 mM NaCl (TBS)+0.1% non-idet NP 40 detergent (TBS/NonI), and blocked with 0.2% bovine serum albumin in coating buffer for 2 hours at 25.degree. C. The wells were washed and primary antiserum of rabbit anti-endonuclease V IgG antibodies (5 ug/ml) were added for 2 hours at 25.degree. C. The wells were washed and primary antiserum of rabbit anti-endonuclese V IgG antibodies (5 ug/ml) were added for 2 hours at 25.degree. C. The wells were washed and secondary anti-serum of goat anti-rabbit IgG antibodies conjugated to alkaline phosphatase were added for 30 minutes at 25.degree. C. The wells were washed and o-nitrophenyl phosphate (1 mg/ml) was added. After 30 min. incubation, the optical densities of the wells were measured at 405 nm. The concentration of enzyme in the liposome preparation was calculated from a standard curve of optical density versus enzyme concentration for the endonuclease V standards.

Detailed Description Text (47):
The results of these experiments are shown in Table I. As shown therein, the PC/DCP/Chol liposomes and the PC/SA/Chol liposomes incorporated similar amounts of enzyme in terms of ug/ml. In terms of enzyme activity, however, the PC/SA/Chol liposomes exhibited over four times the activity of the PC/DCP/Chol liposomes.

Detailed Description Text (61):
The data in this table demonstrate that DNA repair synthesis was increased up to 30% in normal human epidermal keratinocytes treated with liposomes, in a manner proportional to the enzyme concentration contributed by the liposomes. The PG/DCP liposomes required about 10 times the enzyme concentration to achieve the same biologic effect as PC/DCP liposomes. Similar results were achieved with XP12BE cells, with a maximum increase of 82%. The larger effect in XP cells than in normal human cells is expected because in XP cells endo V restores DNA repair blocked by a biochemical defect, whereas in normal human cells endo V augments an already active process. As an additional control unirradiated XP12BE cells were treated with PC/DCP liposomes, but no increase in repair replication was observed.

Detailed Description Text (67):
(1) pH sensitive liposomes are superior to pH insensitive liposomes in delivery of DNA repair enzymes to human cells

Detailed Description Text (74):
Liposomes were prepared from phosphatidylcholine, phosphatidylethanolamine, oleic acid and cholesteryl hemisuccinate in a 2:2:1:5 molar ratio, in the manner described in Example 3 using the molecular sieve technique of Example 3 to isolate

liposomes. The activity of the enzyme entrapped in the liposomes was measured by the activity assay described in Example 3 to isolate liposomes. The activity of the enzyme entrapped in the liposomes was measured by the activity assay described in Example 3 and the enzyme concentration was measured by the ELISA method described in Example 4. As a control, an aliquot of endonuclease V was boiled for 60 minutes and liposomes were prepared a for the native enzyme. The activity assay revealed no active enzyme in the liposomes prepared from boiled endonuclease V. Human cells were grown as described in Example 5, section (1), including the SV40-transformed normal human fibroblast line GM637. Cells were irradiated with the UV-C source described in Example 5.

Detailed Description Text (80):
Human cells were irradiated and treated with either active or inactive endo V encapsulated in liposomes at 0.3 ug enzyme/ml. After 6 hours the DNA was extracted from each sample and the number of pyrimidine dimers per million DNA bass was measured. The results are shown in Table 9. For all cells, including normal human epidermal keratinocytes and SV40-transformed fibroblasts from a normal and an XP patient, treatment with the active endonuclease in liposomes enhanced removal of dimers from DNA by between 25 and 60%. The enhancement was greater in XP cells because the liposomes restored repair which was blocked by the biochemical defect, while in normal cells the liposomes augmented an already active pathway.

Detailed Description Text (87):
Although specific embodiments of the invention have been described and illustrated, it is to be understood that modifications can be made without departing from the invention's spirit and scope. For example, although the invention has been illustrated in terms of DNA damage caused by ultraviolet light, it is equally applicable to DNA damage resulting from other sources, such as ionizing radiation, chemicals producing covalent adducts to DNA, and other deformations of bases or strand breaks. Similarly, in addition to being used after DNA damage has occurred, as in the examples presented above, liposomes containing DNA repair enzymes can be administered prophylactically prior to the time cells will be exposed to conditions under which DNA damage is likely.

Current US Original Classification (1):
424/450

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